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MILUTIN M. MILOSAVLJEVIĆ[1]
IVAN M. VUKIĆEVIĆ[1]
VEIS ŠERIFI[1]
JASMINA S. MARKOVSKI[2]
IVANA STOJILJKOVIĆ[3]
DUŠAN Ž. MIJIN[4]
ALEKSANDAR D. MARINKOVIĆ[4]

[1]Faculty of Technical Science, University of Priština, Kosovska Mitrovica, Serbia
[2]Vinča Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia
[3]Faculty of Chemistry, University of Belgrade, Belgrade, Serbia
[4]Faculty of Technology and Metallurgy, University of Belgrade, Belgrade, Serbia

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OPTIMIZATION OF THE SYNTHESIS OF *N*-ALKYL AND *N,N*-DIALKYL THIOUREAS FROM WASTE WATER CONTAINING AMMONIUM THIOCYANATE

Article Highlights

- Synthesis of *N*-alkyl and *N,N*-dialkyl thioureas are optimized in laboratory
- The optimal laboratory synthesis of thioureas are transferred to semi-industrial level
- Commercial as well as industrial waste materials are used in synthesis of thioureas
- Presented methods are suitable environmentally benign option to existing procedures

Abstract

The optimized methods for N-alkyl and N,N-dialkyl substituted thioureas synthesis starting from ammonium thiocyanates, waste water constituent from the production of tetramethylthiuram monosulfide (TMTS), and alkyl amine, are presented in this work., Thioureas synthesis was developed in two ways: Method I – reaction of the thiocyanate and alkylamine in the presence of hydrochloric acid; Method II – reaction of the thiocyanate with benzoyl chloride following by amine addition in the first step, and base hydrolysis in the second step. The structure of the synthesized compounds was confirmed by IR, ^{1}H- and ^{13}C-NMR and MS instrumental methods, and purity was determined by high-performance liquid chromatography method. It is shown that the proposed methods offer a high degree of conversion and purity of product, absence of by-products and technological applicability at industrial scale. Considering the importance of the tetramethylthiuram disulfide (TMTD) and TMTS as vulcanization accelerators as well as thiourea as the pharmacologically active compounds, it can be said that application of the optimized methods of thiourea synthesis will provide significant improvement in sustainable development and implementation of eco-friendly production technology. The described environmentally benign process of thioureas synthesis represents a suitable option to existing methods.

Keywords: thioureas, optimization, semi-industrial level, thiocyanate.

Thiourea (NH_2CSNH_2) and its derivatives, as well as oxidation products, found large alternative application in different industrial fields. Depending on the starting thiourea compound, used oxidants and pH value of reaction medium, a variety of oxidation products can be produced [1]. Catalytic oxidation by the use of hydrogen peroxide in presence of ruthenium complexes ethylenediaminetetra sulfate produce formamidine disulfide, thiourea dioxide, thiourea trioxide and sulfate [2]. Also, uses of hydrogen peroxide as oxidative agent in reaction with thiourea produces a powerful bleaching agent that has various applications in textile industry [3,4], and as corrosion inhibitors for industrial equipment such as boiler [5,6]. Solution of thiourea in dilute hydrochloric acid is used as a complexing agent for removing scales from boilers [7].

Synthesis of *N*-alkyl (aryl) and *N,N*-dialkyl thioureas, starting from the ammonium thiocyanate and an appropriate amine in water at 80-90 °C [8], was the first step in the overall procedure of obtaining certain 2-aminothiazole derivatives of 4-hydroxy-chromen-2--one. This product was used as inhibitors of enzymes

Correspondence: M.M. Milosavljević, Faculty of Technical Science, University of Priština, Knjaza Miloša 7, 38220 Kosovska Mitrovica, Serbia.
E-mail: vidahem@yahoo.com
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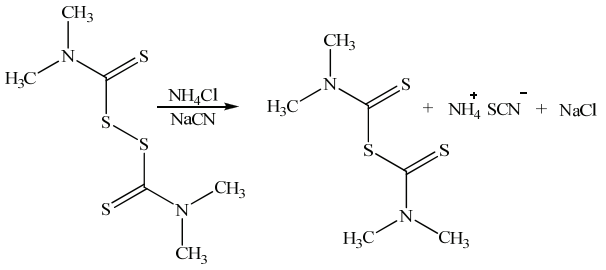
such as kinurenine-3-hydroxylase [9]. Also, *N,N*-dialkyl-*N'*-alkyl thioureas may be prepared from dialkylamine and carbon disulfide in the presence of sodium hydroxide. The sodium salt of dialkyl dithiocarbamic acid was obtained in first reaction step, which by addition of an alkyl amine, and extraction with methylene chloride, gives the corresponding thiourea product [10].

A large number of the methods of thiourea derivatives synthesis has been established: reaction of anilines and sodium isothiocyanate treated with trifluoroacetic acid [11], ammonium thiocyanate in the presence of concentrated hydrochloric acid [12], aroyl isothiocyanates with amines followed by basic hydrolysis of *α*-aroyl-*β*-phenylthiourea product [13], tetraisothiocyanatosilane with primary and secondary amines [14], thioureas with long chain alkyl amines at 170–180 °C, alkyl or aryl isothiocyanates with amine and carbon disulfide and amines [15]. Also, thiourea derivatives have been obtained by reaction of alkyl isothiocyanates with ammonia or amines [16], as well as reaction of carbon disulfide and primary amines in the presence of mercury acetate [17]. Reaction of disubstituted cyanamides with either hydrogen chloride and LiAlHSH [18] or hydrogen sulfide in the presence of ammonia [19] provided thiourea products. Recently, a new and efficient reagent 1-benzo-triazole-1-carbothioamide used for the preparation of mono and *N,N*-disubstituted thioureas was described. Nucleophilic displacement of benzotriazole from intermediary product by attack of a variety of amines gave corresponding *N,N*-disubstituted thioureas product [20].

Due to its extensive ligands applications in coordination chemistry, the chemistry, structure and potential applications of 1-(acyl/aroyl)-3-(mono-substituted) and 1-(acyl/aroyl)-3,3-(di-substituted) thioureas have been overviewed recently [21]. A series of *N*-aroyl-*N'*-substituted thiourea derivatives have been prepared in good to excellent yields under the condition of solid-liquid phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst [22]. Also, *N*-benzoyl-*N'*-carboxyl substituted thiourea derivatives have been synthesized by the reaction of benzoyl isothiocyanate with amino acids, and preliminary biological tests showed excellent plant growth promotion activities [23]. Carbamoyl isothiocyanates can be used for synthesis of 1,3-disubstituted and 1,1,3-trisubstituted thiourea derivatives in reaction with alkyl or aryl amines. A secondary amine can be coupled to the carbamoyl thiourea using EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide). This way, the formation of 1,3-disubstituted and 1,1,3-trisubstituted guanidines through either stepwise or one-pot synthesis was achieved [24].

Several new thiourea and urea derivatives were prepared in satisfactory yield by the reaction of 4-amino-pyrazoles with substituted isothiocyanates or isocyanates in acetone [25]. In reaction of dimethylamine, carbon disulfide and hydrogen peroxide, an aqueous suspension of TMTD product was obtained [26,27]. Industrial process for the TMTS synthesis was performed by reaction of TMTD with cyanide ion and in such way ammonium thiocyanate was released according to the following reaction [28]:



TMTS was obtained as filtration cake while the collected filtrate was an aqueous solution of ammonium thiocyanate [29], which was chosen to be used as reactant for thioureas synthesis.

The aim of this work was focused on the optimization of *N*-alkyl and *N,N*-dialkyl thioureas synthesis starting from either commercial ammonium thiocyanate or waste water obtained from TMTS production which contains ammonium thiocyanate and corresponding amines. The first method developed in this paper, Method I, implied a reaction of thiocyanate with the appropriate amines and hydrochloric acid in ethyl acetate. Second method, Method II, was performed by thiocyanate treatment with benzoyl chloride, amines and sodium hydroxide. In order to get highest reaction yield and purity of obtained product, optimization of presented procedures was performed with respect to variable reaction parameters: reaction time, temperature and molar ratio of reactants. The developed optimal technologies at the laboratory level were transferred and implemented at semi-industrial level with previously performed additional optimization of production technology in regards to reactant mole ratio.

EXPERIMENTAL

Two optimized methods (Method I and Method II) for the *N*-alkyl and *N,N*-dialkyl thioureas synthesis were developed at laboratory and semi-industrial level. The optimization of procedures was performed in relation to reaction time, temperature and mole ratio of reactant.

General procedure for the *N*-alkyl and *N,N*-dialkyl thiourea synthesis according to Method I

In a three-necked flask, equipped with magnetic stirrer, dropping funnel, condenser and thermometer, 10.0 ml of 20% water solution of ammonium thiocyanate (0.12 mol) was introduced and heated to 90 °C. Appropriate amine, *i.e.*, methyl amine (11.73 cm^3, 0.10 mol) was added drop-wise with vigorous stirring of reaction mixture during one hour. Reaction took place for 3 h in temperature range 80-90 °C. Dilute hydrochloric acid (1:1) was added in a cooled reaction mixture and stirring was continued for 30 min. Reaction medium was subjected to vacuum for 5 min (10 kPa) followed by immediate addition of ethyl acetate (200 cm^3) and 15 min intensive mixing. The reaction mixture (suspension) was filtered through a Buchner funnel and the ammonium chloride was separated as filtration cake. The upper layer of filtrate, ethyl acetate solution containing *N*-methyl thiourea, was separated from water layer, dried with sodium sulphate and solvent was removed by atmospheric distillation. Pure product was obtained by recrystallization from methanol followed by column chromatography purification (silica gel 60, 230–400 mesh) using benzene/methanol (9:1) as mobile phase. After solvent evaporation and product drying at 50 °C for 10 h, yield of *N*-methyl thiourea was 76.2%, melting point was 203.5 °C, and purity, obtained by HPLC analysis, was 98.9%. All other thioureas were synthesized in an analogous manner to the above described procedure and reaction conditions presented in Table 1.

General procedure for the *N*-alkyl and *N,N*-dialkyl thioureas synthesis according to Method II

In a three-necked flask equipped with magnetic stirrer, dropping funnel, condenser and thermometer, 8.5 ml of 20% water solution of ammonium thiocyanate (0.10 mol) was introduced and heated to 45 °C. Benzoyl chloride (12.90 cm^3, 0.11 mol) was added drop-wise with vigorous stirring of reaction mixture for two hours. After addition of the appropriate amount of alkyl amine reaction took place for 2 h at 45 °C and cooled down to room temperature. Carefully, 15 ml of sodium hydroxide solution (20%) was added to reaction mixture and continued with mixing for 30 min to provide hydrolysis of *N*-benzoyl-*N,N*-dialkyl thiourea. The reaction mixture was filtered through a Buchner funnel giving a filtration cake which contains raw product and collected filtrate of sodium benzoate water solution. Pure product was obtained by recrystallization from methanol followed by column chromatography purification (silica gel 60, 230–400 mesh) using benzene/methanol (9:1) as a mobile phase. After solvent evaporation and drying at 50 °C for 10 h, *N*-methyl thiourea yield was 72.2%, melting point was 202-205 °C, and purity, obtained by performing HPLC analysis, was 98.5%. All other thioureas were synthesized in an analogous manner to above procedure, using the appropriate amine in regards to reaction conditions presented in Table 2.

Additionally, developed procedures were analogously applied in the synthesis of thiourea derivatives starting from real waste water samples collected from the synthesis of TMTS at laboratory level. Calculation of the starting reaction mixture was based on the result of waste water composition: ammonium

Table 1. Reaction conditions, yield, melting point and purity of the product obtained according to Method I starting from model and real water

Product	NH_4SCN (mol)	Amine (mol)	Reaction time h	Reaction temperature °C	Yield, %	Melting point, °C Found (reported) [lit.]	Purity (HPLC method)
Model water sample							
$CH_3NHC(S)NH_2$	0.12	0.10	3.0-4.0	80-90	76.2	203.5 (202-203) [33]	98.9
$(CH_3)_2NC(S)NH_2$	0.12	0.11	4.0-4.5	85-92	71.0	162-165 (163-164) [34]	98.3
$EtNHC(S)NH_2$	0.12	0.10	3.0-4.0	82-88	75.8	111-112 (110-111) [35]	98.6
$Et_2NC(S)NH_2$	0.12	0.12	4.0-4.5	88-92	70.5	98-100 (99.2-100.6) [34]	98.7
$PrNHC(S)NH_2$	0.12	0.10	3.0-4.0	81-86	73.2	108-110 (109) [36]	99.0
$Pr_2NC(S)NH_2$	0.12	0.12	4.0-5.0	88-92	70.0	109-110 [37]	98.8
Real water sample							
$CH_3NHC(S)NH_2$	0.06	0.07	3.0-4.0	80-90	59.5	201-202 (202-203) [33]	97.2
$(CH_3)_2NC(S)NH_2$	0.06	0.06	4.0-4.5	85-92	53.4	161-163 (163-164) [34]	97.3
$EtNHC(S)NH_2$	0.06	0.07	3.0-4.0	82-88	51.8	110-112 (110-111) [35]	98.1
$Et_2NC(S)NH_2$	0.06	0.08	4.0-4.5	88-92	49.7	97-99 (99.2-100.6) [34]	98.0
$PrNHC(S)NH_2$	0.06	0.06	3.0-4.0	81-86	54.6	106-108 (109) [36]	97.9
$Pr_2NC(S)NH_2$	0.06	0.07	4.0-5.0	88-92	47.3	107-109 [37]	97.5

Table 2. Reaction conditions, yield, melting pint and purity of the product obtained according to Method II starting from model and real water

Product	NH_4SCN (mol)	PhCOCl (mol)	Amine (mol)	Reaction time, h	Reaction temperature °C	Yield %	Melting point, °C Found (reported) [lit.]	Purity (HPLC method)
Model water sample								
$CH_3NHC(S)NH_2$	0.10	0.11	0.11	4.0-5.0	40-45	72.2	202-205 (202-203) [33]	98.5
$(CH_3)_2NC(S)NH_2$	0.11	0.10	0.12	5.0-5.5	45-55	68.3	161-164 (163-164) [34]	98.7
$EtNHC(S)NH_2$	0.10	0.11	0.11	4.0-4.5	40-45	72.5	109-111 (110-111) [35]	98.6
$Et_2NC(S)NH_2$	0.10	0.12	0.12	5.0-6.0	50-60	67.8	97.5-99.0 (99.2-100.6) [34]	98.9
$PrNHC(S)NH_2$	0.10	0.11	0.11	4.0-5.0	45-55	71.3	108-111 (109) [36]	99.0
$Pr_2NC(S)NH_2$	0.10	0.12	0.13	5.5-6.0	55-65	66.7	110-111 [37]	98.9
Real water sample								
$CH_3NHC(S)NH_2$	0.05	0.07	0.07	4.0-5.0	40-45	54.7	200-202 (202-203) [33]	97.1
$(CH_3)_2NC(S)NH_2$	0.06	0.06	0.06	5.0-5.5	45-55	48.6	160-163 (163-164) [34]	98.0
$EtNHC(S)NH_2$	0.05	0.07	0.07	4.0-4.5	40-45	49.5	108-110 (110-111) [35]	97.6
$Et_2NC(S)NH_2$	0.05	0.08	0.08	5.0-6.0	50-60	51.2	97-99 (99.2-100.6) [34]	98.2
$PrNHC(S)NH_2$	0.05	0.07	0.07	4.0-5.0	45-55	50.7	105-108 (109) [36]	98.2
$Pr_2NC(S)NH_2$	0.05	0.08	0.08	5.5-6.0	55-65	42.8	108-111 [37]	97.2

thiocyanate 8.9%, sulfate 1.6%, phosphate 0.8% and cations (K, Na, Ca, Mg, Fe, etc.) in overall content of around 2.6%. Results of *N*-alkyl and *N,N*-dialkyl thiourea synthesis are given in Tables 1 and 2. The structure of the synthesized products was confirmed by IR, ^{1}H- and ^{13}C-NMR spectroscopic, and MS spectrometric data (Table 3).

Semi-industrial development of ammonium thiocyanate water solution treatment as by-product from TMTS production plant

A schematic presentation of the developed technology at semi-industrial level for waste water treatment containing ammonium thiocyanate, obtained from TMTS production facility, is given in Figure 1.

Table 3. ^{1}H- and ^{13}C-NMR data, as well as results of elemental and IR analysis of N*-alkyl and* N, N*-dialkylthioureas*

Product	^{1}H-NMR (δ/ ppm)	^{13}C-NMR (δ/ ppm)	Elemental analysis Calculated/Found (%)
$CH_3NHC(S)NH_2$	2.71 (CH_3), 7.46 (NH), 7.08 (NH_2)	30.9 (CH_3), 183.1 (CS)	C 26.65; H 6.71; N 31.08; S 35.57 C 26.52; H 6.78; N 31.22; S 35.48
$(CH_3)_2NC(S)NH_2$	3.05 (CH_3), 7.10 (NH_2)	31.3 (CH_3), 182.9 (CS)	C 34.59; H 7.74; N 26.89; S 30.78 C 34.64; H 7.78; N 26.95; S 30.63
$EtNHC(S)NH_2$	1.19 (CH_2-C<u>H</u>$_3$), 3.51 (C<u>H</u>$_2$-CH_3), 7.49 (NH), 7.11 (NH_2)	14.53 (CH_2-<u>C</u>H_3), 39.12 (<u>C</u>H_2-CH_3), 182.2 (CS)	C 34.59; H 7.74; N 26.89; S 30.78 C 34.54; H 7.71; N 26.80; S 30.95
$Et_2NC(S)NH_2$	1.03 (CH_2-C<u>H</u>$_3$), 3.13 (C<u>H</u>$_2$-CH_3), 7.11 (NH_2)	12.83 (CH_2-<u>C</u>H_3), 41.37 (<u>C</u>H_2-CH_3), 181.6 (CS)	C 45.42. H 9.15. N 21.19; S 24.25 C 45.40; H 9.04; N 21.26; S 24.30
$PrNHC(S)NH_2$	0.81 (CH_2-CH_2-C<u>H</u>$_3$), 1.47 (CH_2-C<u>H</u>$_2$-CH_3), 2.63 (C<u>H</u>$_2$-CH_2-CH_3), 7.51 (NH), 7.10 (NH_2)	10.93 (CH_2-CH_2-<u>C</u>H_3), 21.55 (CH_2-<u>C</u>H_2-CH_3), 43.75 (<u>C</u>H_2-CH_2-CH_3), 181.4 (CS)	C 40.65; H 8.53; N 23.70; S 27.13 C 40.69; H 8.44; N 23.62; S 27.25
$Pr_2NC(S)NH_2$	0.78 (CH_2-CH_2-C<u>H</u>$_3$), 1.31 (CH_2-C<u>H</u>$_2$-CH_3), 2.11 (C<u>H</u>$_2$-CH_2-CH_3), 7.12 (NH_2)	11.78 (CH_2-CH_2-<u>C</u>H_3), 21.05 (CH_2-<u>C</u>H_2-CH_3), 53.75 (<u>C</u>H_2-CH_2-CH_3), 180.53 (CS)	C 52.45; H 10.06; N 17.48; S 20.01 C 52.38; H 10.11; N 17.42; S 20.09
Product	IR, ν_{max} / cm^{-1}		MS (*m*/*z*)
$CH_3NHC(S)NH_2$	3260, 3167 (NH, NH_2), 2924, 2855, 1633 (NH_2), 1557, 1465, 1300, 1152 (C=S), 1127		90
$(CH_3)_2NC(S)NH_2$	3247 (NH_2), 2935, 2865, 1628 (NH_2), 1539, 1499, 1468, 1257, 1064 (C=S), 1048		104
$EtNHC(S)NH_2$	3263, 3169 (NH, NH_2), 2958, 2925, 2853, 1634 (NH_2), 1554, 1464, 1302, 1155 (C=S), 1123		104

Table 3. Continued

Product	IR, ν_{max} / cm^{-1}	MS (*m*/*z*)
$Et_2NC(S)NH_2$	3275, 3174 (NH_2), 2938, 2867, 1630 (NH_2), 1532, 1493, 1461, 1254, 1061 (C=S), 1045	132
$PrNHC(S)NH_2$	3165 (NH, NH_2), 2920, 2851, 1638 (NH_2), 1543, 1462, 1300, 1163 (C=S), 1115 (C=S)	118
$Pr_2NC(S)NH_2$	3277 (NH_2), 2939, 2866, 1631 (NH_2), 1529, 1492, 1459, 1250, 1060 (C=S), 1039 (C=S)	160

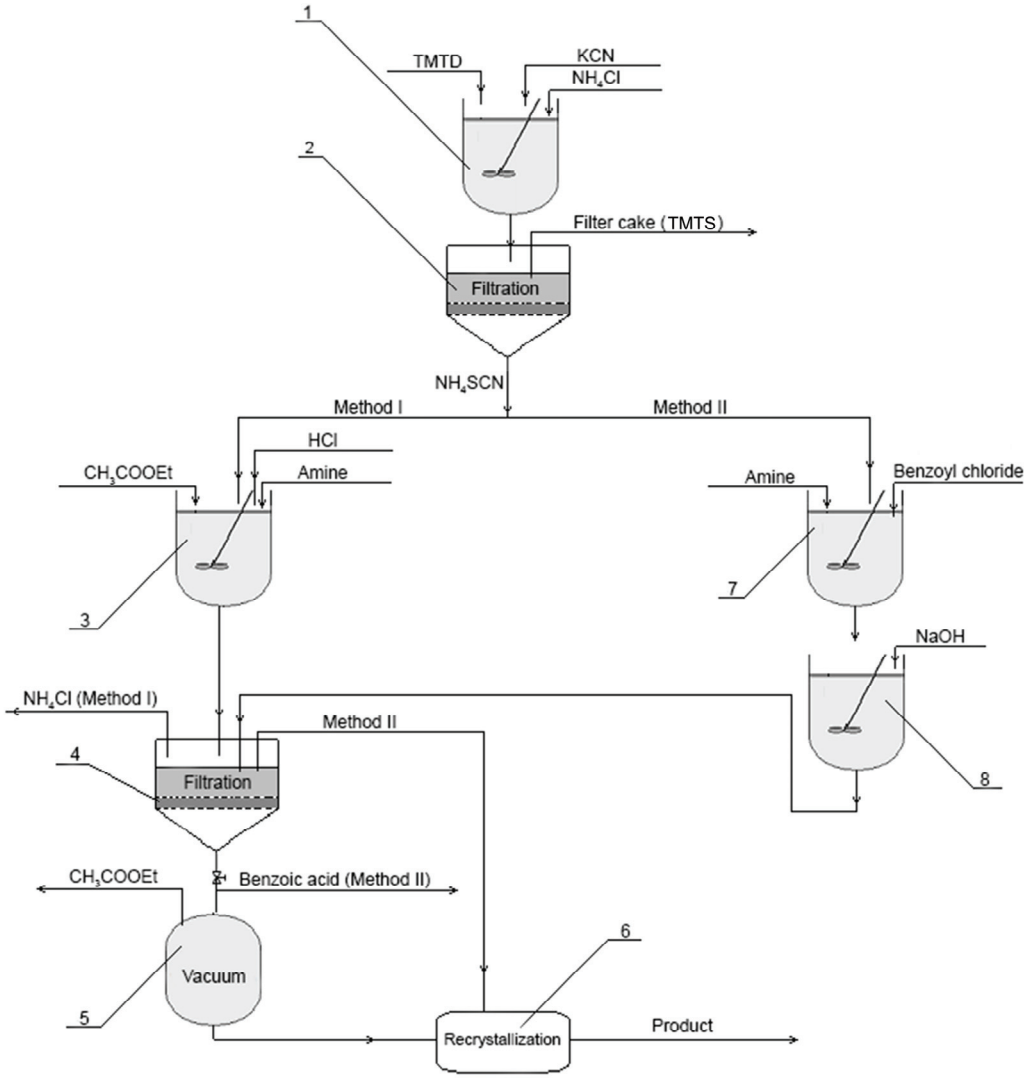


Figure 1. Schematic presentation of semi-industrial production technology of N-alkyl and N,N-dialkyl thioureas.

TMTS is produced by heterolytic cleavage of disulfide bridge present in TMTD by nucleophilic attack of cyanide ion introduced by potassium cyanide in the presence of ammonium chloride as an pH controlling agent (provide pH of reaction mixture in the range 6-7). In the course of the production of TMTS, waste water containing by-product ammonium thiocyanate is inevitably generated. Method for the processing of waste water included filtration and transport to reactor 3 (6 m^3). Treatment of waste water by the Method I was performed by the addition of alkyl amine and hydrochloric acid (Table 4), vacuum treatment (10 KPa) for 10 min and ethyl acetate introduction into reaction mixture. After stirring of reaction mixture at 80-90 °C for 3 h, obtained suspension was filtered through a Buchner funnel (position 4). The filtration cake contained technical ammonium chloride and after purification and drying it could be used as

Table 4. Results of of N*-ethyl and* N,N*-diethyl thiourea synthesis performed at semi-industrial level; reactant: $EtNH_2$ (70%, ρ = 0.88 g/cm³, HCl (15%, ρ = 1.01 g/cm³), $EtOOCCH_3$ (ρ = 0.89 g/cm³), MeOH (ρ = 0.80 g/cm³), PhCOCl (ρ = 1.21 g/cm³), NaOH (20%, ρ = 1.2 g/cm³); Et_2NH (98.5%, ρ = 0.71 g/cm³, HCl (15%, ρ = 1.01 g/cm³), $EtOOCCH_3$ (ρ = 0.89 g/cm³) MeOH (ρ = 0.80 g/cm³), PhCOCl (ρ = 1.21 g/cm³), NaOH (20%, ρ = 1.2 g/cm³)*

Batch/ method	Reactant							Reaction condition		By-product		Product			
	Waste water (m^3)	Ethyl amine (m^3)	HCl (m^3)	Ethyl acetate (m^3)	MeOH m^3	ArCOCl m^3	NaOH m^3	Time h	Tempera-ture, °C	NH_4Cl kg	ArCOOH m^3	Yield kg	Yield %	Purity HPLC	Melting point, °C
N-Ethyl thiourea															
1/Method I	1.0[a]	0.19	0.07	0.60	0.80	-	-	5.0	80-90	96.0	-	140.6	51.4	96.1	111-113[b]
2/Method I	1.0[a]	0.23	0.08	0.60	0.80	-	-	5.1	80-90	99.0	-	153.7	56.2	96.3	110-112[b]
3/Method II	1.0[a]	0.19	-	-	0.80	0.32	0.51	6.0	45-55	-	0.5[c]	144.0	52.7	95.9	110-111[b]
N,N-Diethyl thiourea															
1/Method I	1.0[a]	0.27	0.08	0.60	0.85	-	-	5.5	85-90	95.5	-	134.7	49.3	96.1	97-99[d]
2/Method I	1.0[a]	0.32	0.08	0.60	0.85	-	-	5.7	85-90	98.5	-	137.0	50.4	96.5	98-100[d]
3/Method II	1.0[a]	0.27	-	-	0.85	0.33	0.55	6.5	55-60	-	0.45[c]	124.5	45.6	96.3	97-100[d]
1/Method I	1.0[a]	0.27	0.08	0.60	0.85	-	-	5.5	85-90	95.5	-	134.2	49.1	96.0	97-99[d]

[a]Quantity of ammonium thiocyanate in waste water - 200 kg (20% water solution); [b]literature value of melting point of $EtNHC(S)NH_2$ is 110-111 °C [35]; [c]collected ArCOOH in water solution (concentration 40%); [d]literature value of melting point of $Et_2NC(S)NH_2$ is 97-99 °C (99.2-100.6 °C) [34]

commercial product. Filtrate was consisted from two layers: upper one contained dissolved product in ethyl acetate and lower one was water layer which contained mostly inorganic salts. After separation from water layer, upper layer was dried and subjected to atmospheric distillation to remove ethyl acetate, followed by vacuum distillation applied to evacuate residual solvent and higher boiling materials (position 5). Satisfactory quality for commercial application was achieved by recrystallization (position 6) from methanol producing 140.6 kg (51.4%) and 96.1% purity of *N*-ethyl thiourea, obtained by HPLC analysis (Table 4).

Production of *N*-ethyl thiourea (Method II) was performed by transferring the waste water, containing ammonium thiocyanate, into reactor 7 following by addition of benzoyl chloride and alkyl amine (Table 4). The reaction took place for 2 h at 45 °C, after what reaction mixture was cooled down to room temperature. Addition of 0.51 m^3 (20%) sodium hydroxide and continuation of the mixing for 30 min provided hydrolysis of *N*-benzoyl-*N*-ethyl thiourea (position 8). The reaction mixture was filtered through a Buchner funnel, the water solution of sodium benzoate was collected and filtration cake contained raw product. The raw product was purified by double recrystallization from methanol (position 6) producing 144.0 kg (52.7%) of *N*-ethyl thiourea (HPLC purity 95.9%) (Table 4). Analogous synthesis of *N,N*-diethyl thiourea was performed at semi-industrial level (Table 4).

Instrumental techniques used for structure determination of synthesized compounds

^{1}H- and ^{13}C-NMR measurements were performed on a Varian Gemini 2000 (200/50 MHz) instrument at 25 °C. Chemical shifts (δ) were reported in part per million (ppm) relative to tetramethylsilane (δ_H = 0 ppm) in ^{1}H-NMR, and to deuterated chloroform (δ_C = = 77.2 ppm) in ^{13}C-NMR, using the residual solvent peak as a reference standard. Fourier-transform infrared (FTIR) spectra were recorded in transmission mode using a BOMEM (Hartmann & Braun) spectrometer. All mass spectra were recorded on a Thermo Finnigan Polaris Q ion trap mass spectrometer, including TraceGC 2000 (ThermoFinnigan Corp., Austin, TX, USA). Polaris Q ion trap GC/MS system with EI and DIP (direct insertion probe) techniques was used. DIP mode was used to introduce the sample and EI/MS technique to acquire the spectra. The ionization conditions were: ion source temperature 200 °C, maximum energy of electron excitation 70 eV, corona current 150 μA. The data obtained were processed using Xcalibur™ 1.3 software. HPLC (high performance liquid chromatograph) was performed on Spectra System P4000 equipped with a UV detector, Zorbax SB-C8 column, mobile phase benzene/methanol (HPLC grade) (9:1), isocratic mode. Elemental analysis was performed on the Vario EL III elemental analyzer, and the results of analysis are in good agreement with theoretical values (±0.2%).

The concentration of starting ammonium-thiocyanate in waste water was determined according to two methods: the Vollhard method [30], and method

based on thiocyanate reaction with thioglycolic acid which provide quantitative conversion to *N*-substituted thiocarbamoylmercaptoacetate or 3-substituted rhodamine, a product with characteristic UV absorption [31]. Determination of cations concentrations in water solution from TMTS semi-industrial production plant was performed by the use of inductively coupled plasma mass spectrometry (ICP-MS) using an Agilent 7500ce ICP-MS system (Waldbronn, Germany) and Perkin Elmer Analyst 200, MHS 15 (Waltham, MA, USA). ICP-MS was equipped with an octopole collision/reaction cell, Agilent 7500 ICP-MS ChemStation software, a MicroMist nebulizer and a Peltier cooled (2.0 °C) quartz Scott-type double pass spray chamber. Standard optimization procedures and criteria are specified in the manufacturer's instruction manual. Sulfate was determined by using standard gravimetric method, and phosphate by spectrophotometric method according to the Deniges procedure [32].

RESULTS AND DISCUSSION

In the experimental part of this work, optimal parameters for *N*-alkyl and *N,N*-dialkyl thioureas synthesis (Methods I and II - Experimental) were postulated. In both methods a model and waste water containing ammonium thiocyanate (the latter one is obtained during the synthesis of TMTS) were used in reaction with corresponding amine. Optimal conditions for *N*-alkyl and *N,N*-dialkyl thioureas synthesis were selected on the basis of maxima yield and purity of the product in relation to variable reaction parameters: reaction time, temperature and molar ratio of reactants. The obtained optimal results of *N*-alkyl and *N,N*-dialkyl thioureas synthesis are presented in Tables 1 and 2.

Based on the results given in Tables 1 and 2, it can be observed that high yields and purity of synthesized *N*-alkyl and *N*, *N*-dialkyl thioureas are achieved starting from model and waste water containing ammonium thiocyanate. General consideration of the presented results clearly indicates somewhat higher yields obtained by the use of model water. Such result is obviously a consequence of the presence of interfering ions, which could have a detrimental effect on the reaction yield. The structure of synthesized products was confirmed by IR, ^{1}H-NMR and MS spectrometric data (Table 3).

From the reaction yield and purity of the obtained product, shown in Table 1, it can be concluded that an increase of the amount of the secondary amine over 0.12 mol have no influence on the yield and purity of the synthesized *N*-alkyl and *N,N*-dialkyl thioureas. It may be noted that with the use of secondary alkyl amines, at equimolar ratio of reactants, a negligible increase of the product yield from 70.0 to 71.0% is obtained. Also, it is interesting that if the primary alkyl amine is used, wherein the thiocyanate is in excess, the yield is in the range from 73.2 to 76.2%. Thus, it can be deduced that the higher yield is obtained by reaction of the primary amine with ammonium thiocyanate, while the lowest yield is obtained using dipropylamine as reactant. The longer reaction time, more than six hours, and an reaction temperature increase does not give a higher yield of *N,N*-dialkyl thiourea (Method I).

Based on the data presented in Tables 1 and 2, higher yields of *N*-alkyl and *N,N*-dialkyl thioureas obtained following Method I could be assumed. Similar influences of amine structure on reaction yields is obtained by comparing Methods I and II, while the lowest yield for dipropyl amine (70.0% by Method I and 66.7% by Method II) is observed (Tables 1 and 2). Also, longer reaction time and higher temperature are applied for reaction performed in presence of disubstituted amines.

Analysis of the experimental data indicates that influence of structural features of reacting species, *i.e.* amine effect on the yield of *N*-alkyl and *N,N*-dialkyl-thioureas, could be discussed. Considering stereochemical aspect of amine involved in creation of activated complex indicate a significant influence of the steric effect of the amine alkyl group on the stability of activated complex. The lower yield found in reactions with disubstituted alkyl amines is an indication of the existence of more pronounced repulsive steric interaction of the alkyl groups in the activated complex. More intensive steric repulsion of voluminous alkyl groups presented in the disubstituted amine cause decreasing of the ability of the amine to access to the reaction center, *i.e.*, electrophilic carbon of thiocyanate group. Reduced effectiveness of the amine group to exert a nucleophilic attack caused a decrease in reaction yield. The higher reaction yield of thiourea product obtained by Method I, in comparison to Method II, could be reasonably explained by complexity of the reaction mechanism, due to high reactivity of benzoyl chloride and ability of *N*-benzoyl-*N,N*-dilakyl thiourea to participate in a side reaction (Figure 2). It can be assumed that Method I takes place as a one-step reaction by nucleophilic addition of amine at the thiocyanate group, while in Method II, a multistep reaction mechanism is operative. Nucleophilic attack of the thiocyanate anion to the carbonyl group of benzoyl chloride occurs in the first step of reaction mechanism following by an attack of the

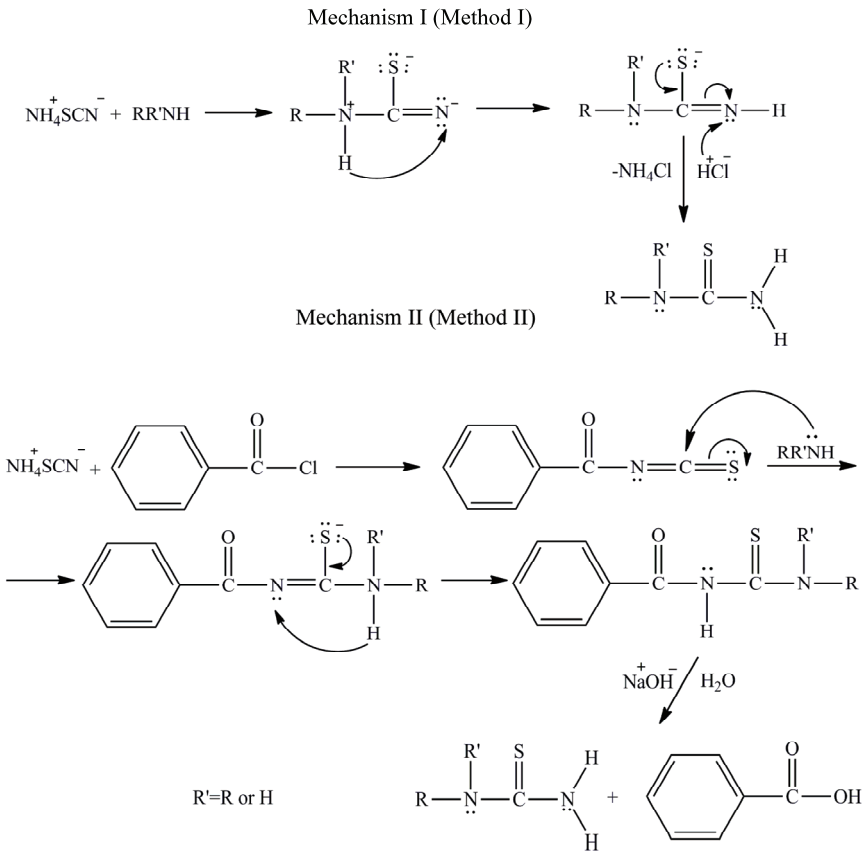


Figure 2. Proposed mechanisms of N*-alkyl and* N,N*-dialkyl thioureas synthesis performed according to Method I and II.*

amine on the thiocarbonyl carbon of the obtained benzoyl thiocyanate in the second step. Basic hydrolysis of the intermediary compound produce benzoic acid and *N*-alkyl and *N,N*-dialkyl thioureas product (Figure 2).

The probable reaction mechanisms of the *N*--alkyl and *N,N*-dialkylthioureas synthesis performed by Method I [8], and Method II, over benzoylthiocyanate intermediary compound and *N*-benzoyl-*N,N*-dilakyl thiourea [13], are presented in Figure 2.

Semi-industrial synthesis of N-ethyl and N,N-diethyl thiourea

Based on the laboratory results of waste water treatment containing thiocyanate from the synthesis of the TMTS (Methods I and II), we transferred developed laboratory technology to semi-industrial level. The described technological procedure of waste water treatment in the production of the TMTS actually represents a new technological process for the alkyl tioureas synthesis using waste water from the production of the TMTS and the TMTD, which contains the ammonium thiocyanate. The results of semi-industrial synthesis of *N*-ethyl and *N,N*-diethyl thiourea, from ammonium thiocyanate present in the waste water from the production plant of TMTS, are summarized in Table 4.

The defined synthetic procedure, Method I, is applied in Batches 1 and 2 (Table 4). In comparison to Batch 1, where the thiocyanate excess of the 20% is used and 51.4% yield is achieved, equimolar ratio of the reactants increased yield to 56.2% in Batch 2. However, as a result of Method II, reaction yield of Batch 3 is lower than Batch 2, where Method I is used. Identical reaction conditions presented in Table 4 are applied in a pilot-plant production of *N,N*-diethyl thiourea (Table 4). It can be seen that the lower yields is achieved in all three batches with *N,N*-diethyl thiourea in regards to the yields of pilot-plant synthesis of *N*-ethyl thiourea (Table 4). On the basis of the results obtained by the semi-industrial production process it can be concluded that a) wastewater from the production TMTS's can be treated in two ways, b) significant conversion is achieved (over 45%) in all of the three batches shown in Table 4 and the final commercial products of *N*-ethyl and *N,N*-diethylthiourea are the high level of purity determined by the HPLC method, c) the structure of the isolated components and all of the synthesized products are confirmed by instrumental methods.

Developed optimal methods offers good alternative technology for industrial exploitation in production of *N*-alkyl and *N,N*-dialkylthiourea from commercial ammonium thiocyanate, or more preferably from waste water containing this reactant obtained from TMTS production plant. From an ecological point of view, both facts related to use waste water as the reaction medium and by-product ammonium thiocyanate as reagent in the synthesis of *N*-alkyl and *N,N*--dialkyl thioureas, indicate that such technology is highly favorable to be implemented at semi-industrial level. These environmentally friendly and simple processes, with short reaction times, represent a suitable option to existing methods. This concept contributes to the remarkable effectiveness and economic benefit of the implemented optimal laboratory procedure at the semi-industrial level.

CONCLUSION

The results presented in this work describe an optimal procedure for the laboratory and semi-industrial synthesis of *N*-alkyl and *N,N*-dialkyl thioureas. The developed processes, presented by Method I and Method II, start from either model or waste water containing ammonium thiocyanate. High purity and satisfactory yield of *N*-alkyl and *N,N*-dialkyl thioureas synthesis were obtained by applying optimal Methods I and II in both laboratory and semi-industrial level. Based on the high degree of conversion and purity of the obtained compounds it was possible to perform transfer (scale-up) of the optimal laboratory synthesis of *N*-alkyl and *N,N*-dialkyl thioureas to semi-industrial level. The new procedure of the optimal *N*-alkyl and *N,N*-dialkyl thioureas achieves significant improvements in terms of product yield and purity, process duration and simplicity as well as low impact to the environment. These results strongly indicate the usefulness of the presented methods for synthesis of thiourea derivatives starting from commercial as well as industrial waste material.

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MILUTIN M. MILOSAVLJEVIĆ[1]
IVAN M. VUKIĆEVIĆ[1]
VEIS ŠERIFI[1]
JASMINA S. MARKOVSKI[2]
IVANA STOJILJKOVIĆ[3]
DUŠAN Ž. MIJIN[4]
ALEKSANDAR D. MARINKOVIĆ[4]

[1]Fakultet Tehničkih Nauka, Univerzitet u Prištini, Kosovska Mitrovica, Srbija
[2]Institut za Nuklearne nauke Vinča, Univerzitet u Beogradu, Beograd, Srbija
[3]Hemijski Fakultet, Univerzitet u Beogradu, Beograd, Srbija
[4]Tehnološko-Metalurški fakultet, Univerzitet u Beogradu, Beograd, Srbija

NAUČNI RAD

OPTIMIZACIJA POSTUPAKA SINTEZE *N*-ALKIL- I *N,N*-DIALKILTIOUREA IZ OTPADNE VODE KOJA SADRŽI AMONIJUM-TIOCIJANAT

Optimizovane metode za sintezu N-alkil- i N,N-dialkiltiourea, koje polaze iz amonijum--tiocijanata, koji se nalazi u otpadnoj vodi iz proizvodnje tetrametiltiuram-monosulfida (TMTS), i alkilamina, prikazane su u ovom radu. Osvojene su dve metode sinteze tiouree: Metoda I – reakcija tiocijanata u prisustvu hlorovodonične kiseline; Metoda II – reakcija tiocijanata sa benzoil-hloridom nakon čega sledi dodavanje odgovarajućeg amina u prvom koraku, i bazne hidrolize inermedijera u drugom koraku. Struktura sintetisanih tiourea je potvrđena na osnovu podataka iz IR, ^{1}H- i ^{13}C-NMR, kao i MS spektara, a čistoća je potvrđena primenom metode tečne hromatografije pod visokim pritiskom. Pokazano je da se primenom optimalnih metoda dobijaju visoki prinosi i čistoća proizvoda, a usled odsustva sporednih proizvoda metode su primenjive na industrijskom nivou proizvodnje. Uzimajući u obzir značaj tetrametiltiuram-disulfida (TMTD) i TMTS kao ubrzivača vulkanizacije i tiouree kao potencijanih farmakološki aktivnih jedinjenja, može se konstatovati da će primena optimizovanih metoda sinteze tiouree obezbediti značajna poboljšanja u primeni zelenih tehnologija u proizvodnoj praksi, kao i doprineti održivom razvoju. Opisani procesi sinteze tiourea imaju mali uticaj na životnu sredinu i zbog toga predstavljaju prihvatljive opcije za primenu u odnosu na postojeće metode sinteze tiourea.

Ključne reči: tiourea, optimizacija, polu-industrijski nivo proizvodnje, tiocijanat.